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Full Length Article

Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared to vitamin K antagonists

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ABSTRACT

Introduction: Rivaroxaban is a convenient oral anticoagulant for patients with venous thromboembolism (VTE). The impact of rivaroxaban and vitamin K antagonists (VKAs) on abnormal uterine bleeding (AUB) in real life has not been previously explored.
Materials and methods: We performed a single-center retrospective study on AUB in female VTE patients of reproductive age who were treated with either rivaroxaban or VKAs.
Results: Questionnaire results were available for 52 patients in each treatment group.
Approximately two thirds of all women reported AUB after initiation of anticoagulant therapy. Patients using rivaroxaban were more likely to experience prolonged (>8 days) menstrual bleeding (27 % *vs.* 8.3%, P = 0.017). Rivaroxaban treatment increased the duration of menstrual bleeding from median 5 (IQR 3.5-6.0) days before start of treatment to 6 (IQR 4.1-8.9) days (P < 0.001). VKA treatment did not lead to significant prolongation of the menstrual period.
Patients on rivaroxaban more frequently reported an unscheduled contact with a physician for AUB than women using VKAs (41% *vs.* 25%, P = 0.096). They also reported increased need for menorrhagia-related medical or surgical intervention (25% *vs.* 7.7%, P = 0.032) and had more adaptations of anticoagulant therapy (15% *vs.* 1.9%, P = 0.031).
Conclusion: AUB is frequent after initiation of anticoagulant therapy for acute symptomatic VTE. Compared to VKAs, rivaroxaban was associated with prolonged menstrual bleeding and more medical interventions and adaptation of anticoagulant treatment for AUB. These data can guide proactive discussion with patients starting anticoagulant therapy.

1. Introduction

Venous thromboembolism (VTE) is a frequent disorder, affecting 1–10 per 10,000 women of reproductive age per year [1,2]. The two main clinical presentations are deep-vein thrombosis (DVT) and pulmonary embolism (PE). Therapy typically consists of initial treatment with low-molecular-weight heparins (LMWHs) followed by vitamin K antagonists (VKAs) for a period of at least 3 months. The need for long-term secondary prevention depends on the presence or absence of modifiable or non-modifiable risk factors [3]. Recently, direct-acting oral anticoagulants (DOACs) offer an alternative convenient treatment for patients with VTE. These drugs act through direct inhibition of thrombin (dabigatran) or activated factor X (rivaroxaban, apixaban, edoxaban). Phase III trials have demonstrated that DOACs were as effective as VKAs while associated with less major bleeding. DOACs offer an important advantage because laboratory monitoring and subsequent dose adjustment are not necessary, contrary to therapy with VKAs [4].

Rivaroxaban has been licensed for the treatment and secondary prevention of VTE and was reimbursed for VTE in Belgium in January 2013. Its efficacy and safety have been proven in the EINSTEIN-DVT and -PE studies that showed non-inferiority for recurrent VTE and a significant reduction in major bleeding rate [5–7]. In the setting of non-valvular atrial fibrillation, there was a shift in bleeding pattern, with fewer intracranial hemorrhages and higher gastrointestinal bleeding rates amongst the patients treated with rivaroxaban compared to warfarin [8,9]. A different bleeding pattern may also be present for urogenital bleedings. Currently, there are no specific data regarding the effect of rivaroxaban

Abbreviations: AUB, abnormal uterine bleeding; BMI, body mass index; DVT, deep-vein thrombosis; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LMWH, low-molecular-weight heparin; DOAC, direct-acting oral anticoagulant; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

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on abnormal uterine bleeding (AUB). The objective of our study was to evaluate the impact of rivaroxaban compared to VKAs on AUB in women with acute symptomatic VTE.

2. Materials and Methods

We conducted a single-center retrospective study at the University Hospital of Leuven, Belgium. The study was approved by the institutional review board. All women between the age of 14 and 55 years who were enrolled in the VTE care program from September 2007 until September 2014 were evaluated for eligibility. Patients who did not have an acute symptomatic VTE, but suffered from asymptomatic thrombosis, thrombophilia or superficial thrombophlebitis were excluded from the study, as well as those who were treated with an anticoagulant other than rivaroxaban or VKAs. One hundred nineteen patients gave written informed consent for review of their medical records and filled out a questionnaire appropriately. The questionnaire is available in the Supplementary Appendix.

We collected information on baseline biometric parameters and VTE risk factors at the time of the index VTE. Recent immobilization was defined as being bedridden during more than half of the time for a duration of at least three consecutive days in the past four weeks or as having a recent self-reported significant reduction in physical movement. Use of estrogen included use of estrogen containing combined contraceptives, selective estrogen receptor modulators and in vitro fertilization therapy. The puerperium was defined as a period of 8 weeks starting from delivery. Malignancy was defined as active malignancy or having had treatment within a period of six months prior to the diagnosis of VTE [10,11]. Thrombophilia included proven resistance to activated protein C, protein S and protein C deficiency, antithrombin deficiency, prothrombin G20210A mutation, elevated factor VIII, the presence of a lupus anticoagulant and/or anticardiolipin antibodies. A positive familial history of VTE was defined as a history of PE or DVT in a first or second degree relative.

We defined AUB according to the recommendations of the International Federation of Gynecology and Obstetrics (FIGO) as prolonged menstrual bleeding (more than 8 days in duration on a regular basis), intermenstrual bleeding, heavy menstrual bleeding (passage of blood clots) or menstrual blood loss causing anemia or requiring unscheduled contact with a medical practitioner, medical or surgical intervention or adaptation of anticoagulant therapy [12]. We also assessed if the change in menstrual bleeding pattern interfered with activities of daily life.

We assessed the presence of anemia as well as other manifestations of increased bleeding tendency, e.g. epistaxis, ecchymoses, hematuria and gastrointestinal blood loss. Anemia was defined according to the World Health Organization definition as a serum haemoglobin level of less than 12 mg/dL or, in the absence of an available in-hospital laboratory analysis, as self-reported anemia or need for transfusion [13]. Iron deficiency was concluded upon iron replacement therapy.

Data on unscheduled contact(s) with a medical practitioner, medical or surgical intervention or adaptation of anticoagulant treatment because of menstrual bleeding were collected. We defined an unscheduled contact as a consultation with a physician or a hospitalization specifically for AUB. A medical or surgical intervention was defined as change of oral hormonal or contraceptive therapy (e.g. implantation of an intrauterine device), endometrial ablation/embolization or hysterectomy.

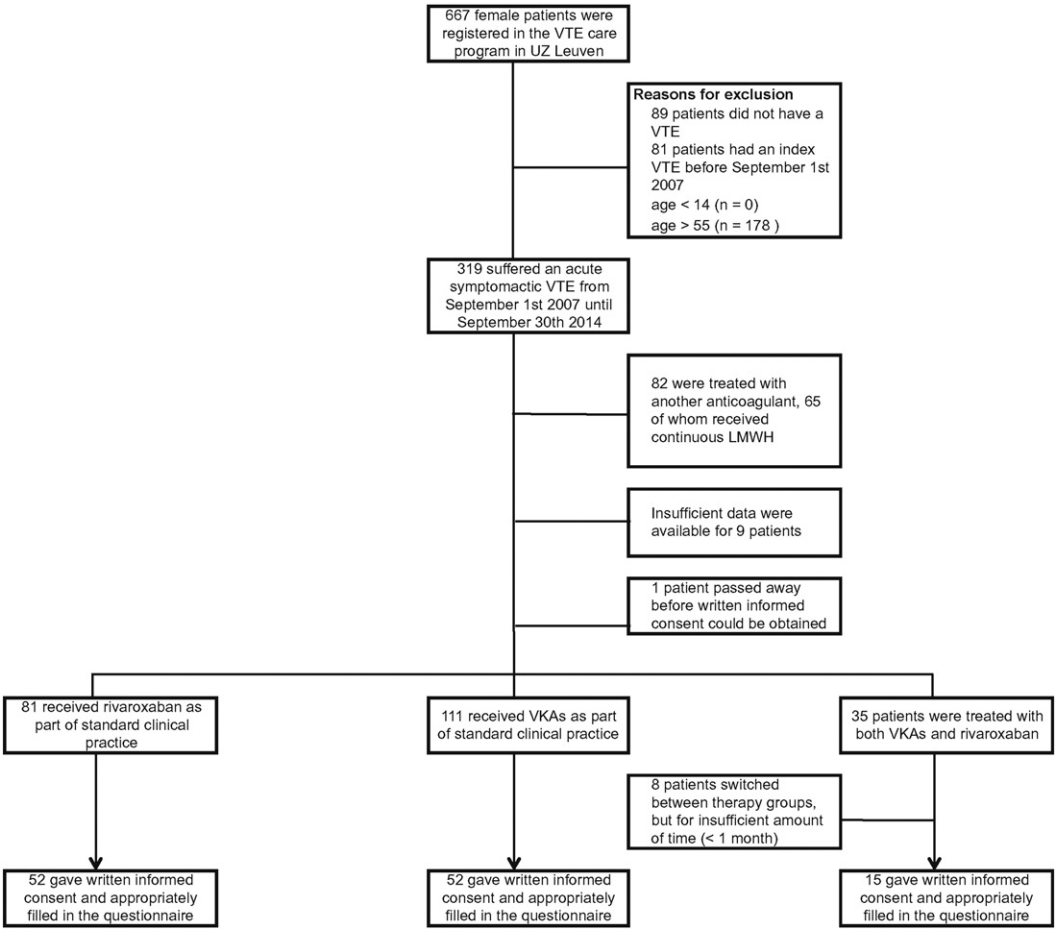

Fig. 1. Study population. VTE denotes venous thromboembolism, LMWH = low-molecular-weight heparins, VKA = vitamin K antagonists.